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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/693,558	10/20/2000	Elfi Biedermann	25846-0003	7777

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EXAMINER	
SPIVACK, PHYLLIS G	

ART UNIT	PAPER NUMBER
1614	17

DATE MAILED: 07/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/693,558	Applicant(s) BIEDERMANN ET AL.	
	Examiner Phyllis G. Spivack	Art Unit 1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 August 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32-56* is/are pending in the application.

4a) Of the above claim(s) *37,41-49,51 and 52* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-36, 38-40, 50, 53-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Applicants' Response filed August 22, 2003, Paper No. 16, is acknowledged. New claims 53-56 are presented. Accordingly, claims 32-56 are now pending. In response to the restriction requirement set forth in Paper No. 13, Applicants elected Group I directed to methods for preventing, reducing or eliminating side effects, or neutralizing the side effects, of a cancerostatic or immunosuppressive agent, comprising administering a compound having vitamin PP activity of formulae II, IIa, IIb, III, IIIa, IIIb, IIIc, IV, IVa, IVb, V, Va or Vb, wherein no additional heterocyclic ring systems or sugars are present. Further, in response to an election of species requirement, Applicants elected the species where:

(1) the compound having vitamin PP activity or prodrug thereof is nicotinamide, a compound of formula V, where b is 1, and R^{21}, R^{22}, R^{23}, R^{26} and R^{27} are all hydrogen; and

(2) the compound of formula 1 is N-[4-(1-benzoylpiperidin-4-yl)-butyl]-3-(pyridin-3-yl)-acrylamide, a compound where each of $R^{-1(i)}$, $R^{2(i)}$, $R^{3(i)}$ and $R^{4(i)}$ is hydrogen, k is 0, $A^{(i)}$ is -CH=CH-, $D^{(i)}$ is-$(CH_2)_4$-, E is piperidin-4-yl, and G is 1-benzoyl.

The restriction requirement is proper and is maintained.

The subject matter under consideration remains those methods of use for preventing, reducing or eliminating side effects, or neutralizing the side effects, of a cancerostatic or immunosuppressive agent comprising administering a compound having vitamin PP activity of formulae II, IIa, IIb, III, IIIa, IIIb, IIIc, IV, IVa, IVb, V, Va or Vb, wherein no additional heterocyclic ring systems or sugars are present, claims 32-36, 38-40, 50 and 53-56. Pharmaceutical compositions, claims 41-49, 51 and

52. Those methods of use comprising administering compounds with additional heterocyclic ring systems or sugars for R^{25} of formulae IV, IVa, or IVb, and claim 37, are withdrawn from consideration by the Examiner, 37 CFR 1.142(b), as being directed to non-elected inventions.

A list of co-pending and related cases is requested when Applicants respond to this Office Action.

Claims 32-40 were rejected in the last Office Action under judicially created doctrine as being drawn to an improper Markush group. Upon reconsideration, this rejection is withdrawn.

In the last Office Action claims 33-36 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that applicants regard as the invention with respect to the recitation for R^{27} in claim 33, "their thioxo analogs", which lacks antecedent basis, and the recitation "anionic salts" at the end of claim 33, which was confusing.

In response applicants have clarified the terms "thioxo analogs" or "thioxo derivatives" to mean the replacement of the C=O groups with the corresponding C=S analogs in claims 32, 33, 35, 41, and 46; and replaced the terms "anionic salts" with the terms "pharmaceutically acceptable salts" in claim 33, 35, 41 and 46.

The rejection under 35 U.S.C. 112, second paragraph, is withdrawn.

In the last Office Action claims 32-36 were rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is

most nearly connected, to make and/or use the invention. The recitation within the definition of R^{25} in claim 33 "such that the alcohol $R^{25}(OH)_a$" fails to define the invention properly. There is no alcohol depicted in formulae IV, IVa and IVb. The recitation within the definition of R^{27} "in which a methylene group is optionally replaced by O, NH or N-alkyl" does not disclose the site at which the replacement occurs. Further, the terminal R^{27} cannot be O or NH.

In response, applicants urge the phrase "such that the alcohol $R^{25}(OH)_a$" defines R^{25} is the residue of the alcohol $R^{25}(OH)_a$ in claims 33 and 41. Applicants argue in the art of organic synthesis alkylene groups having a methylene group can be readily replaced with a heteroatom such as O, NH or N-alkyl, and in claim 33, when b is 2, then R^{27} is not a terminal group, and R^{27}can be O or NH.

Applicants' arguments are persuasive. This rejection of record under 35 U.S.C. 112, first paragraph, is withdrawn.

Claims 32-36, 38-40 and 53-56 were rejected under 35 U.S.C. 112, first paragraph, in the last Office Action as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are directed to the preventing, reducing or eliminating side effects, or neutralizing the side effects, of a cancerostatic or immunosuppressive agent comprising administering a compound having PP activity. The specification provides support on pages 110-115 for neuralization of the growth-inhibiting effect of an anti-tumor

substance, K22.097, by administration of nicotinic acid or nictoinamide in human leukemia cells, in normal leukocytes, in primary intestine cells and in NMRI mice.

Attention is directed to In re Wands, 8 USPQ2d 1400 where the court set forth factors to consider when assessing whether or not a disclosure would require undue experimentation. These factors are:

1) the quantity of experimentation necessary

2) the amount of direction or guidance provided

3) the presence or absence of working examples

4) the nature of the invention

5) the state of the art

6) the relative skill of those in the art

7) the predictability of the art and

8) the breadth of the claims.

The instant specification fails to provide guidance that would allow the skilled artisan background sufficient to practice the instant invention without resorting to undue experimentation in view of further discussion below.

The nature of the invention, state of the prior art, relative skill of those in the art and the predictability of the art

The claimed invention relates to preventing, reducing or eliminating side effects or neutralizing the side effects of a cancerostatic or immunosuppressive agent comprising administering a compound having PP activity.

The relative skill of those in the art is generally that of a Ph.D. or M.D. with expertise in the field of oncology.

Each particular neopastic or immunologic disease or disorder has its own specific characteristics and etiology. The unpredictability observed with single agent therapy is compounded when a combination of agents is employed. The broad recitation "preventing, reducing or eliminating side effects or neutralizing the side effects of a cancerostatic or immunosuppressive agent" is inclusive of many pathologies that presently have no established successful therapies.

It is clear the art to which the present invention relates is highly unpredictable and unreliable with respect to conclusions drawn from laboratory data extrapolated to clinical efficacy.

The breadth of the claims

The claims are very broad and inclusive of any side effect of any cancerostatic or any immunosuppressive agent comprising administering a plethora of disclosed compounds having PP activity.

The amount of direction or guidance provided and the presence or absence of working examples

The working examples are limited to the administration of the anti-tumor substance K22.097 and nicotinamide or nicotinic acid in laboratory models using cells from a human monocytic leukemia, normal lymphocytes, cryptic cells of the large intestine or in NMRI mice.

The quantity of experimentation necessary

Applicants have failed to provide guidance as to which particular compound having PP activity in combination with which particular cancerostatic or immunosuppressive agent would be preferred for preventing, reducing or eliminating side effects or neutralizing which particular side effects. The skilled artisan would expect the interaction of a particular combination of drugs in the treatment of a particular side effect to be very specific and highly unpredictable absent a clear understanding of the structural and biochemical basis for each agent. The instant specification sets forth no such understanding or any criteria for extrapolating beyond the combination of the single anti-tumor substance K22.097 and nicotinamide or nicotinic acid. Even for the combinations set forth, no direction is provided to prevent or eliminate a side effect. Only neutralization under a specific set of conditions is clearly supported. Absent reasonable *a priori* expectations of success for using a particular chemotherapeutic combination to prevent or eliminate any particular side effect following administration of a cancerostatic or immunosuppressive agent, one skilled in the oncology or immunology art would have to test extensively many combinations of agents to discover which particular type of side effect responds to that particular combination. Since each prospective embodiment, as well as future embodiments as the art progresses, would have to be empirically tested, undue experimentation would be required to practice the invention as it is claimed in its current scope. The specification provides inadequate guidance to do otherwise.

Claims 32-36 were rejected under 35 U.S.C. 102(a) as being anticipated by Budihardjo et al., Clinical Cancer Research in the last Office Action. It was asserted

aminonicotinamide, which can be metabolized in vivo to a compound with vitamin PP activity, as a modulator of the action of various antineoplastic treatments.

Applicants argue Budihardjo teaches that 6-aminonicotinamide (6AN) increases the sensitivity of human cancer cells to cisplatin, but Budihadjo does not teach or suggest the use of any agent to protect non-tumor cells, which is an important aspect of reducing the side effects of cancerostatic or immunosuppressive agents such as cisplatin therapy.

Applicants' arguments have been given careful consideration but are not found persuasive. The rejection is repeated for reasons of record. As a "modulator of the action of various antineoplastic treatments", it would have been reasonable to expect any number of functional and morphological cellular changes would occur that alter in a positive way the side effect profile of a cancerostatic or immunosuppressive agent.

In the last Office Action claims 32-36 were rejected under 35 U.S.C. 102(b) as being anticipated by Artemov, V.A., Vopr. Eksp. Klin. Immunol. (abstract). It was asserted Artemov teaches the administration of 5-hydroxy-6-methyl-3, 4-pyridinemethanol, a compound of instant formula II, pyridoxine, to reduce the immunodepressive side effect of the cancerostatic agent 6-mercaptopurine.

Applicants argue Artemov teaches that pyridoxine negates the immunodepressive effect of 6-mercaptopurine when given in optimal doses, which suggests that the method reduces the immunodepressive effect on an immunodepressant, but the study does not show or suggest any methods for preventing, reducing or eliminating the side effects caused by the agent.

No distinction is seen between the terms "immunosuppressive" in the present claims and "immunodepressive" in Artemov's teaching. Because pyridoxine reduced the immunodepressive effect of 6-mercaptopurine, a side effect, the rejection of claims 32-3 under 35 U.S.C. 102(b), as being anticipated by Artemov, is maintained.

No claim is allowed.

Any inquiry concerning this communication should be directed to Phyllis Spivack at telephone number 571-272-0585.

Spivack/tgd

June 24, 2004

Phyllis Spivack

PHYLLIS SPIVACK
PRIMARY EXAMINER

Application Number	Application No.	Applicant(s)	
	09/693,558	BIEDERMANN ET AL.	
	Examiner	Art Unit	
	Phyllis G. Spivack	1614	